IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
BETH ANNE PIPER
APPLICATION NO: 09/460,920
FILED: DECEMBER 14, 1999
FOR: METHOD FOR TREATING DIABETES

Art Unit: 1614
Examiner: R. Cook

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF BURTON RODNEY IN SUPPORT OF DECLARATION OF PRIOR INVENTION OF BETH ANNE PIPER TO OVERCOME CITED U.S. PATENT NO. 6,303,146 (37 C.F.R. § 1.131)

To the Commissioner of Patents and Trademarks:

1. This Declaration is submitted in support of the Declaration of Prior Invention in the United States of Beth Anne Piper to Overcome Cited U.S. Patent No. 6,303,146 (37 C.F.R. § 1.131).

2. I, Burton Rodney, declare as follows:

3. I was employed as a full time patent attorney for Bristol-Myers Squibb Company and its predecessors from March, 1972 to April, 2000.

4. From October, 1999 to December 14, 1999 I drafted and filed a patent application covering the use of a low dose metformin/glyburide combination in the first-line treatment of diabetes.

5. Beth Anne Piper is the inventor of the use of a low dose metformin/glyburide combination in the first-line treatment of diabetes, a description of her conception of which is set out in an e-mail to me dated August 3, 1999 (identified as ATTACHMENT 1).

6. The actual date of conception of Beth Anne Piper's invention as claimed in the subject application was prior to July 15, 1998 as set out in Paragraph 6 of her Declaration of Prior Invention, which accompanies this Declaration.

7. The drafting of the subject application from October, 1999 to its filing less than 2.5 months later on December 14, 1999 is evidence of due diligence in the constructive reduction to practice of the invention claimed in the subject application.

Further Declarant sayeth not.

Burton Rodney

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-4336

Date: January 23, 2003

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of application Serial No. 09/460,920 or any patent issued thereon.

Burton Rodney

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
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Date: January 23 2003

Subject: fixed combo met/gly
Date: Tue, 03 Aug 1999 09:46:54 -0400
From: "Beth A Piper" <piperb@bms.com>
Organization: Bristol-Myers Squibb
To: Burton Rodney <burton.rodney@bms.com>

Bud -

The fixed combo started out as a line extension for glucophage. Traditionally with diabetes therapies, combination therapy has only been indicated for second line use, after a monotherapy has been found to be inadequate or no longer controlling a patiet's blood sugar.

The concept of a fixed combination metformin/glyburide is not novel, it is marketed in 6-12 countries by various manufacturers. Both glyburide and metformin are older than I am but there is little to no data available on fixed combination use, I actually could only find two studies. the dosing is typically 400-500 mg of metformin with 2.5-5 mg of glyburide/glibenclimide or some other sulfonylurea.

When BMS approached the FDA about doing a fixed combination for second line therapy (with a 500/2.5 mg and 500/5 mg), the FDA replied that they wanted a firstline therapy trial as well. As it would be a single entity that might get used as first line or 'monotherapy' they wanted to know it would be safe in a different patient population or the population that did not yet require combination therapy for glycemic control. Approval depended upon safety trends as firstline therpy.

Not only was fixed combinaiton data hard to find but there was no data on combination therapy available as firstline treatment. From clinical experience I knew the planned dosing was too high for first line use and that we would see too much hypoglycemia compared to monotherapy. We then halved the 500/2.5 to get a 250/1.25 mg tablet strength. I knew it would work for glucose lowering and should be safe but didn't know how it would compare to monotherapy.

We couldn't have asked for better results. We beat placebo but were also statistically better than both glyburide monotherapy and metformin monotherapy with respect to glycemic efficacy. We have postive safety trends that the FDA was interested in, we are doing ad-hoc ananalysis in the ISS for both hypoglycemia and GI SE, We also got unexpected data that suggests that metformin has a postive or glucose sensitiziing effect on the pancreas. It is getting late I'll give you the deatils later.

Beth

Read and Understood
R Q Rodney April 3, 1999

SE = side effects

ATTACHMENT 1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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DECLARATION OF PRIOR INVENTION OF BETH ANNE PIPER IN THE UNITED STATES TO OVERCOME CITED U.S. PATENT NO. 6,303,146 (37 C.F.R. § 1.131)

To the Commissioner of Patents and Trademarks:

1. This Declaration is to establish reduction to practice of the invention in this application in the United States at a date prior to July 14, 1999, that is, the effective date of U.S. Patent No. 6,303,146 (cited by the Examiner) as a reference and prior to July 15, 1998, that is the priority date claimed in U.S. Patent No. 6,303,146.

2. I, BETH ANNE PIPER, declare as follows:

3. That I am the inventor of the invention claimed in U.S. patent application Serial No. 09/460,920 filed December 14, 1999.

4. That the invention described in the Claims as filed and in Claims 37, 45 to 54, 58 to 60, 71 to 73 and 75 to 79 of application Serial No. 09/460,920 was conceived by me in the United States prior to July 15, 1998.

5. That the various teams at Bristol-Myers Squibb Company involved in the development of a low dose metformin/glyburide combination exercised due diligence in the United States prior to July 15, 1998, the priority date of U.S. Patent No. 6,303,146, and prior to July 14, 1999, the filing

date in the United States of U.S. Patent No. 6,303,146 in an actual reduction to practice of the invention on or about November 24, 1999 and exercised due diligence in a constructive reduction to practice with the filing of the subject application on December 14, 1999.

6. That prior to July 15, 1998 I informed the Project Working Group (PWG) at Bristol-Myers Squibb Company dealing with "Metformin/Glyburide Combination Tablet" that the first-line therapy protocol (CV138-019) involving the clinical testing of a metformin/glyburide combination in first-line therapy of patients having diabetes should be revised to reduce doses of glyburide to avoid hypoglycemia while still retaining required efficacy. I proposed a revised regimen based on a 12-week period of low dose combination of metformin and glyburide of 250 mg metformin and 1.25 mg glyburide for use in established diabetics (diet and exercise failures). My conception of and proposal that a low dose combination of metformin/glyburide should be employed in the first-line treatment of established diabetics is my conception of the invention as claimed in the subject application and is set out in the PWG Minutes of a meeting held prior to July 15, 1998, a copy of relevant parts of which are attached including page 2, paragraph D. entitled "Revising the 1st-Line Therapy Protocol (CV138-019)" and a copy of each of two "Overheads Used in Discussion of 1st-Line Protocol for Glyburide Combination Tablet" namely, Overhead entitled "CV138-019-Firstline Combination Therapy" and Overhead entitled "Combination Metformin-Glyburide-Clinical Utility" wherein I disclosed a low dose combination of metformin/glyburide 250 mg/1.25 mg. These relevant pages are identified as Attachments A, B and C, respectively.

7. That prior to July 15, 1998, but about one month after the PWG meeting reported in paragraph 6 above, it was reported to the PWG that tablet #4, which had a Glyburide C_{max} ratio to Hoechst's Daoril of 1.49 and a Glyburide AUC ratio to Hoechst's Daoril of 0.91, would be proposed to the FDA for clinical use under Bristol-Myers Squibb's existing IND. The above is set out in the PWG Minutes of a meeting held prior to July 15, 1998, but after the meeting reported on in paragraph 6 hereof, a copy of relevant parts of which are attached hereto and referred to as ATTACHMENT D.

It was also reported at this meeting that "the development of a lower-dose tablet (250/1.25) is being accelerated . . . ." I reported that "the clinical outline has been prepared and is ready to be sent to the FDA for comment. Attached is a copy of the clinical outline submitted to the FDA covering a low dose metformin/glyburide product for first-line therapy in Type II diabetes patients and is identified as ATTACHMENT D-1.

All of the above demonstrates due diligence in reducing the invention to practice.

8. That prior to July 15, 1998 and approximately one month after the PWG meeting reported on in paragraph 7 above, a PWG meeting was held. The minutes of this meeting indicate that a letter was sent to the FDA informing the FDA that protype formulation #4 (tablet #4 in

paragraph 7) would be employed. A proposed outline for a first-line therapy study was also included in the FDA letter. The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT E sets out relevant portions of the minutes of the above PWG Meeting including the above description of the FDA letter.

9. That prior to July 15, 1998 and approximately one month after the PWG meeting reported on in paragraph 8 above, another PWG meeting was held. The minutes of this meeting indicate that the FDA responded positively to the proposal to use prototype formulation #4 for clinical studies but the FDA requested that the first-line trial have an additional 12-week period (stable dose). The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT F sets out relevant portions of the minutes of the above PWG Meeting including a description of the above.

10. That prior to July 15, 1998 and approximately one month after the PWG meeting reported on in paragraph 9 above, another PWG meeting was held. The minutes of this meeting indicate that the first-line trial for metformin/glyburide would be conducted as two separate trials. The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT G sets out relevant portions of the minutes of the above meeting including an outline of first-line trials.

11. That prior to July 15, 1998 and approximately one month after the PWG meeting reported on in paragraph 10 above, another PWG meeting was held. The minutes of this meeting indicate that supply estimates for the first-line therapy study were finalized and that a protocol for such study was approved and would be forwarded to investigators. The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT H sets out relevant portions of the minutes of the above meeting.

12. That prior to July 15, 1998 and approximately one-two months after the PWG meeting reported on in paragraph 11 above, another PWG meeting was held. The minutes of this meeting indicate that a date for trial commencement was chosen and that an investigators' meeting was scheduled and 116 sites were recruited. The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT I sets out relevant portions of the minutes of the above meeting.

13. That prior to July 15, 1998 and approximately one month after the PWG meeting reported on in paragraph 12 above, another PWG meeting was held. Internal draft notes of the meeting indicate that an investigators' meeting for the first-line clinical trial was held and that a date for start of the study was set. The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT J sets out relevant portions of the internal draft notes.

14. That prior to July 15, 1998 and approximately one month after the PWG meeting reported on in paragraph 13 above, another PWG meeting was held. The minutes of this meeting

indicate that the FDA requested a change to the first-line therapy protocol and that an amendment to the protocol would be prepared. The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT K sets out relevant portions of the minutes.

15. That prior to July 15, 1998 and approximately one month after the PWG meeting reported on in paragraph 14 above, another PWG meeting was held. The minutes of this meeting indicate that discussions were held with the FDA regarding the first-line study protocol (CV138-019, referred to as -019). The minutes also indicate that "the -019 study is progressing . . . and enrollment is scheduled for completion by September 30, 1998 . . . . Every effort is being made to achieve the enrollment objectives." The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT L sets out relevant portions of the minutes.

16. That prior to July 15, 1998 and approximately one month after the PWG meeting reported on in paragraph 15 above, another PWG meeting was held. The minutes of this meeting indicate that there was a safety study with the metformin/glyburide combination tablet and the -019 study enrollment was progressing. The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT M sets out relevant portions of the minutes.

17. That prior to July 15, 1998 and approximately one month after the PWG meeting reported on in paragraph 16 above, another PWG meeting was held. The minutes of this meeting indicate that "study recruitment for the -019 study is 50% of expected randomized to date" and that there will be 150 sites and "abbreviated investigators' meetings are planned." The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT N sets out relevant portions of the minutes.

18. That on or about July 28, 1998, a PWG Meeting was held. The minutes of this meeting indicate that enrollment in the first-line study -019 "is progressing well and we anticipate completion by the end of September . . ." and that comparative dissolution studies with the 250/1.25 and 500 2.5 tablets will be conducted. The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT O sets out relevant portions of the minutes.

19. That on or about August 25, 1998, a PWG Meeting was held. The minutes of this meeting indicate that enrollment in the first-line study -019 "is progressing well and we anticipate completion by the end of September . . . ." The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT P sets out relevant portions of the minutes.

20. That on or about September 25, 1998, a PWG Meeting was held. The minutes of this meeting indicate that enrollment in the first-line study –019 "is progressing well and we anticipate completion ahead of schedule." Comparative dissolution studies between the 250/1.25 and 500/2.5 tablets were proposed. Stability studies were being carried out. The above demonstrates due

diligence in reducing the invention to practice. ATTACHMENT Q sets out relevant portions of the minutes.

21. That on or about October 27, 1998, a PWG Meeting was held. The minutes of this meeting indicate that "the -019 (first-line therapy) enrollment has been completed on schedule . . . . and that comparative dissolution studies between the 250/1.25 and 500/2.5 tablets is proposed. A meeting with the FDA in early November is planned to discuss these and other issues." The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT R sets out relevant portions of the minutes.

22. That on or about November 24, 1998, a PWG Meeting was held. The minutes of this meeting indicate that preliminary data from the open-label (low dose 250/1.25) -019 study (first-line therapy in patients who are drug naïve and inadequately controlled with diet and exercise)

> "in which patients were directly enrolled into open-label, show that patients treated with the metformin/glyburide combination for 13 weeks have a Hemoglobin A1c value of 6.8% compared with a baseline value of 10.3%; in the same study, fasting glucose levels drop from a baseline value of 267 mg/dl to 162 mg/dl at two weeks, and 144 mg/dl at week 13. These dramatic results are expected to have a significant impact on medical opinion."

ATTACHMENT S sets out relevant portions of the minutes.

The above together with paragraphs 7 to 21 demonstrate conception of the invention and a reduction to practice prior to the effective date of the cited U.S. Patent No. 6,303,146, namely, prior to July 14, 1999.

Alternatively, the above together with paragraphs 7 to 21 demonstrate conception of the invention prior to the July 15, 1998 priority date of U.S. Patent No. 6,303,146 coupled with due diligence from prior to July 15, 1998 to a reduction to practice on or about November 24, 1998.

23. That from December, 1998 through August, 1999 the first-line study -019 continued. Evidence of continued due diligence is set out in Metformin Clinical Working Group Minutes of December 21, 1998 (ATTACHMENT S-1), January 18, 1999 (ATTACHMENT S-2), March 15, 1999 (ATTACHMENT S-3), April 20, 1999 (ATTACHMENT S-4), and May 18, 1999 (ATTACHMENT S-5), as well as in Metformin DCT (Drug Control Manufacture Team) Minutes of June 23, 1999 (ATTACHMENT S-6) and July 21, 1999 (ATTACHMENT S-7).

24. That on August 3, 1999, I sent an e-mail to Burton Rodney, patent attorney at Bristol-Myers Squibb Company (assignee of the subject application), where I indicate that I conceived of the use of a low dose metformin/glyburide combination in first-line therapy for diabetics. ATTACHMENT T is a copy of my August 3, 1999 e-mail communication to Burton Rodney.

25. That on or about August 31, 1999, a PWG Meeting was held. The minutes of this meeting indicate that

> "the -019 final study report, the label, the ISE and the ISS are near completion and should be in Regulatory early next week. We are still on track for a September 30 NDA filing. Given the quality of the results described in the NDA filing and their medical importance, it is reasonable to believe that we stand a good chance of getting priority review by the FDA.
>
> *Action:* Intensive effort will continue to ensure a September filing."

ATTACHMENT T-1 sets out relevant portions of the minutes.

26. That on or about September 28, 1999, a PWG Meeting was held. The minutes of this meeting indicate under the heading "Metformin Glyburide Combination Tablet" that

> "the 52 volume submission and 2 CD-Rom discs are almost complete and will be shipped out on Sept. 30 for filing in Washington. The medical importance of the results described in the NDA filing should qualify this filing for Priority Review. We will know the decision of the FDA when their 45 day review is complete."

In a post-meeting note it is stated that "the NDA was filed on Sept. 30." ATTACHMENT U sets out relevant portions of the minutes.

Copies of the cover page and Introduction section of the NDA filed on September 22, 1999 covering the use of a low dose combination of metformin and glyburide in the first-line therapy of diabetes, together with pages 190 to 212 covering "Formulation Development History", are attached hereto as ATTACHMENT U-1.

As seen on page 197 of Attachment U-1, it is indicated that "prototype 4 was targeted for use in the clinical program". Prototype 4 describe a metformin/glyburide combination tablet containing 500 mg metformin and 2.5 mg glyburide where the glyburide had a particle size (μm) as follows:

"	μm
D25%	6
D50%	11
D75%	19"

On page 201 of Attachment U-1, it is indicated that "the lower strength metformin hydrochloride-glyburide 250 mg/125 mg tablet was manufactured using the same granulation employed for metformin hydrochloride-glyburide tablets 500 mg/2.5 mg, but in this case the granluation was compressed at half the press weight."

27. That from October, 1999 to December 14, 1999, Burton Rodney, patent attorney employed by Bristol-Myers Squibb Company, prepared a patent application covering a low dose metformin/glyburide combination for use in first-line therapy of diabetes and method and filed such patent application with the U.S. Patent and Trademark Office on December 14, 1999, which is a constructive reduction to practice of the invention covered by the claims of the subject application.

A copy of Mr. Rodney's Declaration to this effect accompanies this Declaration.

28. This declaration is submitted prior to Final Rejection.

The undersigned declares further that all statements made herein of her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of application Serial No. 09/460,920 or any patent issued thereon.

BETH ANNE PIPER

Date: 2/1/03